 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#18/Appeal Brief mailed 9/5/02

In re Application of:

Maes et al.

Serial No.: 09/578,361

Filed: May 24, 2000

For: METHOD OF PARALLEL SCREENING FOR INSERTION MUTANTS AND A KIT TO PERFORM THIS METHOD

Examiner: T. Strzelecka

Group Art Unit: 1656

Attorney Docket No.: 4409US

NOTICE OF EXPRESS MAILING

Express Mail Mailing Label Number: EV092481875US

Date of Deposit with USPS: August 19, 2002

Person making Deposit: Jon Wentz

BRIEF ON APPEAL

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Attention: Board of Patent Appeals and Interferences

Sirs:

This brief is submitted in TRIPLICATE pursuant to 37 C.F.R.§ 1.192(a) and in the format required by 37 C.F.R. § 1.192(c):

(1) REAL PARTY IN INTEREST

The real party in interest in the present pending appeal is Vlaams Interuniversitair Instituut Voor Biotechnologie VZW, assignee of the pending application as recorded with the United States Patent and Trademark Office on January 24, 2002 at Reel 012543, Frame 0303.

(2) RELATED APPEALS AND INTERFERENCES

Neither the appellant, the appellant's representative nor the assignee is aware of any pending appeal or interference which would directly affect, be directly affected by or have any bearing on the Board's decision in the present pending appeal.

(3) STATUS OF THE CLAIMS

Claims 1-17 and 19-22 stand rejected.

No claims are allowed.

The rejections of claims 1-17 and 19-22 are being appealed.

(4) STATUS OF AMENDMENTS

An amendment under 37 C.F.R. § 1.116 was filed on June 12, 2002 subsequent to an Advisory Action mailed March 20, 2002. Amendments to claims 1 and 19 were entered. The amendments and analysis of the rejections were submitted in order to overcome the Examiner's rejections raised under 35 U.S.C. § 103(a). An Advisory Action mailed July 5, 2002 notified appellants that the amendment had not overcome the Examiner's Section 103 rejections.

(5) SUMMARY OF THE INVENTION

The invention of the present application comprises a method for simultaneous screening (Specification, p. 2, lines 8-10) for one or more gene insertion mutants in a population of any organism (*Id.*, p. 6, lines 3-4). The method comprises preparing an insertion element mutant library from the population of the organism (*Id.*, p. 6, lines 5-6) in a 3-D array of block, row and column pools (*Id.*, p. 7, lines 28-29 and Figure 1A). The library includes a plurality of nucleic acid insertion

elements (*Id.*, p. 10, lines 20-22) and insertion element flanking sequences (*Id.*, p. 10, lines 11-12) that originate from the population of the organism. (*Id.*, p. 10, lines 18-19).

Each insertion element flanking sequence in the plurality of insertion element flanking sequences (*Id.*, p. 3, lines 26-27) from the block, row and column pools are amplified (*Id.*, p. 6, lines 7-8) using at least one primer derived from a sequence of the nucleic acid insertion element (*Id.*, p. 6, lines 27-28). Amplification products representing the insertion element flanking sequences from the block, row and column pools (*Id.*, p. 6, lines 7-8) are fixed to a solid support as a target for hybridization (*Id.*, p. 6, lines 9-11).

In another aspect, the present invention includes a method for parallel simultaneous screening (*Id.*, p. 2, lines 8-10) for one or more gene insertion mutants in a population of any organism (*Id.*). In this aspect, an insertion element mutant library is prepared in a 3-D array of block, row and column pools (*Id.*, p. 13, lines 23-24) from the population of the organism (*Id.*, p. 6, lines 5-6). The library includes insertion element flanking sequences (*Id.*, p. 10, lines 11-12) that originate from the population of the organism (*Id.*, p. 10, lines 18-19) and flank a plurality of nucleic acid insertion elements (*Id.*, p. 10, lines 11-12) within the organism's genome (*Id.*, p. 8, lines 3-4).

Each insertion element flanking sequence in the plurality of insertion element flanking sequences (*Id.*, p. 3, lines 26-27) is amplified using at least one primer derived from a sequence of the nucleic acid insertion element (*Id.*, p. 6, lines 27-28) from the block, row and column pools (*Id.*, p. 6, lines 7-8). Amplification products representing the insertion element sequences from the block, row and column pools are labeled (*Id.*, p. 6, lines 12-14) and used as probes to hybridize to a gene library organized in a two dimensional array fixed on a solid support (*Id.*, p. 16, lines 14-18 and Figure 1C).

(6) ISSUES

A. Whether claims 1-3, 7, 9-11, 19, 20 and 22 are patentable under 35 U.S.C. § 103(a) over U.S. Patent 6,013,486 ("Dellaporta") in combination with Koes et al., Targeted gene inactivation in petunia by PCR-based selection of transposan insertion mutants, Proc. Natl. Acad. Sci., Vol. 92, pp. 8149-8153, 1995 ("Koes et al.").

B. Whether claim 4 is patentable under 35 U.S.C. § 103(a) over Dellaporta in combination with Koes et al., and further in view of Souer et al., A general method to isolate genes tagged by a high copy number transposable element, The Plant Journal, Vol. 7, pp. 677-685, 1995 ("Sour et al.").

C. Whether claims 5, 6, 8 and 12 are patentable under 35 U.S.C. § 103(a) over Dellaporta in combination with Koes et al., and further in view of Vos et al., AFLP: a new technique for DNA fingerprinting, Vol. 23, pp. 4407-4414, 1995 ("Vos et al.").

D. Whether claims 13-17 and 21 are patentable under 35 U.S.C. § 103(a) over Dellaporta in combination with Koes et al.

(7) GROUPING OF CLAIMS

The grouping of the claims is as follows:

Group I: Claims 1-3, 7, 9-11, 20 and 22

Claims 1-3, 7, 9-11, 20 and 22 do not stand together with the other claims. Claims 2-3, 7, 9-11, 20 and 22 do not fall with claim 1, as it is asserted that claims 2-3, 7, 9-11, 20 and 22 are separately patentable from claim 1 and from each other.

Group II: Claim 4

Claim 4 does not stand together with the other claims. Claim 4 does not fall with claim 1, as it is asserted that claim 4 is separately patentable from claim 1.

Group III: Claims 5, 6, 8 and 12

Claims 5, 6, 8 and 12 do not stand together with the other claims. Claims 5, 6, 8 and 12 do not fall with claim 1, as it is asserted that claims 5, 6, 8 and 12 are separately patentable from claim 1 and from each other.

Group IV: Claims 13-17

Claims 13-17 do not stand together with the other claims. Claims 13-17 do not fall with claim 1, as it is asserted that claims 13-17 are separately patentable from claim 1 and from each other.

Group V: Claims 19 and 21

Claims 19 and 21 do not stand together with the other claims. Claim 21 does not fall with claim 19, as it is asserted that claim 21 is separately patentable from claim 19.

(8) ARGUMENT

(i) 35 U.S.C. § 112, first paragraph

There are no rejections or issues under 35 U.S.C. 112, first paragraph.

(ii) 35 U.S.C. § 112, second paragraph

There are no rejections or issues under 35 U.S.C. 112, second paragraph.

(iii) 35 U.S.C. § 102

There are no rejections or issues under 35 U.S.C. 102.

(iv) 35 U.S.C. § 103

Group I

Claims 1-3, 7, 9-11, 20 and 22 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Dellaporta in combination with Koes et al. (*See*, Final Office Action, mailed December 19, 2001 at page 2).

M.P.E.P. § 706.02(j) sets forth the standard for a Section 103(a) rejection:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success.

> Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Also, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." (*In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)).

The cited references fail to teach or suggest each and every limitation of independent claim 1 and thus, do not render the claims of the present invention obvious. With regard to the Dellaporta reference, a method for selecting insertion events in a genome (*See*, Dellaporta, Col. 2, lines 2-3) is disclosed where DNA is isolated from a population of individuals, pooled and non-selectively amplified (*See, Id.* at Col. 3, lines 50-67). Dellaporta does not teach or suggest an insertion element library built into a 3D-array of block, row and column pools as required by claim 1. Rather, Dellaporta is limited to a "2x2 grid, [where] pools of DNA are then prepared from all of the individuals within each column and row... [a]lternatively, pools needn't be used." (*Id.*, at Col. 15, lines 66-67 and Col. 16, line 3).

Also, Dellaporta does not teach or suggest "amplifying **each of said plurality of insertion element flanking sequences** from said block, row and column pools" as presently claimed by the appellants in claim 1. Rather, the amplification methods in Dellaporta are limited to "using a single primer set [that] may amplify a representative **sample** of insertion junctions from a particular group of individuals." (*Id.*, Col. 12, lines 6-8) (Emphasis added). As further stated in Dellaporta "[a] preferred population [of individuals] will represent a large number of insertional mutants such that there will be a high probability of identifying a mutant for any given locus within the population." (*Id.*, Col. 3, lines 54-58.) Dellaporta does not amplify **all** of the insertion element flanking sequences in the insertion element mutant library, but rather is limited to amplifying **a representative sample** of the library.

Turning now to the Koes et al. reference, a procedure to isolate mutants in which a specific gene with a known sequence is inactivated from a population is disclosed. (*See*, Koes et al., Abstract). Koes et al. does not teach "amplifying **each of said plurality of insertion element flanking sequences** from said block, row and column pools" as presently claimed by the appellants'

claim 1. Rather, Koes et al. is limited to amplifying insertion events in a **specific gene**. As stated in Koes et al., "[o]nly if a transposan is inserted into the gene will a suitable template be generated" because the amplification step uses "a gene-specific and a transposan specific primer." (*Id.*, at 8150).

Therefore, neither Dellaporta nor Koes et al., alone or in combination, teach all of the claim limitations of independent claim 1 because neither reference teaches "amplifying each of said plurality of insertion element flanking sequences from said block, row and column pools" and Dellaporta does not disclose an insertion element library built into a 3D-array of block, row and column pools. Since the cited references fail to teach each and every limitation of pending claim 1, a *prima facie* case of obviousness has not been established. (35 U.S.C. § 103(a)).

The Examiner is improperly combining the Dellaporta and the Koes et al. references because no suggestion or motivation exists to combine the teachings of Dellaporta and Koes et al. as suggested by the Examiner. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." (M.P.E.P. § 2143.01, *citing In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) (Emphasis in original)). The Examiner indicated that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to have used the DNA pooling method of Koes et al. in the insertion element library screening method of Dellporta" and "[t]he motivation to do so, expressly provided by Koes et al. would have been that three-dimensional was less laborious (single round of screening), less liable to detect false positives and identified single plants directly." (Final Office Action at page 4). The motivation provided by the Examiner to combine Dellaporta and Koes et al. does not suggest a desirability for combining the references, but merely restates why Koes et al. prefers a "one-step three-dimensional screening over the three repeated rounds of one-dimensional screening." (Koes et al., at 8152).

The combination of the references is also improper because Dellaporta teaches away from Koes et al. It is improper to combine references where the references teach away from their combination. (*In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction

divergent from the path that was taken by the applicant." (*In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994)). Dellaporta specifically discourages the use of the teachings of Koes et al. As stated in Dellaporta, mutant identification systems where "transposan-induced mutations are isolated for known gene sequences by the general strategy known as 'site-selected' mutagenesis... rel[ying] on the power of PCR to amplify a collection of specific junction fragments between an inserted element and a known target gene sequence... have had limited success in applications toward large-scale genomic investigations" and "the need for individual amplifications of each gene being investigated represents a **significant hindrance** when seeking to identify more than a small number of insertional mutants." (Dellaporta, Col. 1, lines 35-41 and lines 54-60) (Emphasis added). In discouraging the use of "site-selected" mutagenesis systems, Dellaporta specifically refers to the "site selected" approach of Koes et al. which was "used to identify insertion mutations in Petunia, using the tranposan dTph1 (Koes et al. 1995)." (*Id.* at lines 45-47).

The specific teaching away in Dellaporta would discourage a person of ordinary skill in the art from combining the teachings of Dellaporta with the teachings of Koes et al. Since Dellaporta does "in fact teach away from [Koes et al.], then that finding alone can defeat [an] obviousness claim." (*Winner Internation Royalty Corp. v. Wang*, 202 F.3d 1340, 53 USPQ2d 1580, 1587 (Fed. Cir. 2000)). Therefore, a *prima facie* case of obviousness has not been established with respect to independent claim 1 because there is no suggestion or motivation to combine the teachings of the cited references. (35 U.S.C. § 103(a)).

With respect to dependent claims 2, 3, 7, 9-11, 20 and 22, they are allowable at the very least as depending from nonobvious independent claim 1. If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. (*In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)).

Group II

Dependent claim 4 was rejected over Dellaporta in combination with Koes et al. as applied to claims 1 and 3, and further in view of Souer et al. (*See*, Final Office Action at page 4).

A *prima facie* case of obviousness has not been established with regard to claim 4 because each and every limitation of claim 4 is not taught by the cited references. Claim 4 is directed to

reamplifying the at least one amplifyable genomic fragment of claim 3. As stated by the Examiner "neither Dellaporta nor Koes et al. teach reamplifying at least one amplifiable genomic fragment." (*Id.*). Further, Souer et al. does not teach preparing an insertion element mutant library built in a 3D-array of block, row and column pools as required in claim 1, and none of the cited references teach the limitation of amplifying each of the plurality of insertion flanking sequences from the block, row and column pools of claim 1.

The cited references also do not suggest or motivate combining or modifying the cited references to render claim 4 obvious. Dellaporta and Koes et al. do not suggest or motivate reamplifying the at least one amplifiable genomic fragment as required by claim 4 and Souer et al. does not suggest or motivate amplifying each of the plurality of insertion flanking sequences from the block, row and column pools. The motivation relied on by the Examiner recites "it would have been obvious to one of ordinary skill in the art at the time of the invention to have used the re-amplification of Souer et al. in the combined method of Dellaporta and Koes et al. The motivation to do so, expressly provided by Souer et al., would have been that re-amplification improved the yield of amplification of dTph1 flanking sequences." (*Id.*, page 5). However, "the level of skill in the art cannot be relied upon to provide the suggestion to combine references." (M.P.E.P. § 2143.01, *citing Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161, 1171 (Fed. Cir. 1999)). Accordingly, since the cited references do not teach or suggest all of the limitations of claim 4 and do not suggest or motivate a combination of the references, a *prima facie* case of obviousness has not been established.[1] (35 U.S.C. § 103(a)).

Group III

Claims 5, 6, 8 and 12 were rejected under 35 U.S.C. § 103(a) over Dellaporta in combination with Koes et al., and further in view of Vos et al. (*See*, Final Office Action at page 5).

Claim 5 is not rendered obvious because each and every limitation of claim 5 is not taught or suggested by the cited references. Claim 5 is directed to using transposan display amplification

[1] Dependent claim 4 is also allowable at the very least as indirectly depending from nonobvious claim 1. (*See, In re Fine, supra*).

to amplify the insertion element flanking sequences from the insertion element mutant library. As stated by the Examiner "[n]either Dellaporta nor Koes et al. teach [*e.g.*] amplification by transposan display amplification." (*Id.*). Further, Vos et al. does not teach or suggest transposan display amplification, but rather Vos et al. teaches a DNA fingerprinting technique called AFLP. (*See*, Vos et al., Abstract).

Turning now to dependent claim 6, a *prima facie* case of obviousness has not been established because the cited references do not teach or suggest all of the limitations of claim 6. Claim 6 depends from claim 5 and recites the steps used in the transposan display amplification of claim 5. As stated by the Examiner, since "[n]either Dellaporta nor Koes et al. teach amplification by transposan display amplification," Dellaporta and Koes et al. do not teach the elements of claim 6. (Final Office Action at page 5). Further, Vos et al. does not teach each limitation of claim 6 since Vos et al. does not disclose using primers with sequences based on the insertion element sequences as required in claim 6. Rather, as stated in Vos et al., "[f]ingerprints are produced without prior sequence knowledge using a limited set of generic primers." (Vos et al. at page 4407). Since the cited references do not teach or suggest all of the limitations of dependent claim 6, a *prima facie* case of obviousness has not been established. (35 U.S.C. § 103(a)).

Since each and every limitation of claims 5 and 6 are not taught or suggested by the cited references, a *prima facie* case of obviousness may not be established unless the cited references disclose a desirability to modify the teachings of the cited references to result in the claimed invention of dependent claims 5 and 6. (*See*, *In re Fritch*, 922 F.2d 1260, 23 USPQ.2d 1780 (Fed. Cir. 1992)). However, Dellaporta and Koes et al. do not suggest or motivate the use of transposan display amplification and Vos et al. does not suggest or motivate preparing an insertion element mutant library built in a 3D-array of block, row and column pools or fixing a set or nucleic amplification products to a solid support as a target for hybridization.

The Examiner's purported motivation for combining the teachings of Vos et al. with Dellaporta and Koes et al. is "[t]he motivation to do so, expressly provided by Vos et al., would have been that amplification and isolation of DNA fragments was achieved without the prior knowledge of their sequences." (Final Office Action at page 6). However, the amplification and re-amplification steps of claim 6 require primers based on a sequence of the insertion element, while

the primers in Vos et al. are generic. (*See*, Vos et al. at page 4407). Therefore, one of skill in the art would not have a reasonable expectation of success by combining the AFLP method of Vos et al. with the screening methods disclosed in Dellaporta or Koes et al. Accordingly, a *prima facie* case of obviousness has not been established with regard to claims 5 and 6, or claims 8 and 12 depending therefrom.[2] (35 U.S.C. § 103(a)).

Group IV

Claims 13-17 were rejected under 35 U.S.C. § 103(a) over Dellaporta in combination with Koes et al. (*See*, Final Office Action at page 6).

Claims 13-17 are directed to a kit for performing the method of claim 1. The Examiner indicated that "[r]eagent kits for performing DNA assays were conventional in the field of molecular biology at the time of the invention" and "it would have been obvious to one of ordinary skill in the art at the time of the invention to have packaged the insertion element mutant library and amplified insertion element flanking sequences into a kit." (Final Office Action at page 7). However, neither Dellaporta nor Koes et al. suggest or motivate the use of a kit, and as stated by the Federal Circuit "[t]he mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the **desirability** of the modification." (*In re Gordon*, 733 F.2d 900, 221 USPQ 1125, 1127 (Fed. Cir. 1984) (Emphasis added). Also, "the level of skill in the art cannot be used as the suggestion or motivation to combine references." (M.P.E.P. § 2143.01, *supra*). Therefore, without a suggestion or motivation in the cited references to modify the teachings of the cited references, a *prima facie* case of obviousness has not been established with regard to claims 13-17.[3] (35 U.S.C. § 103(a)).

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[2] Since claims 5, 6, 8 and 12 depend, directly or indirectly, from claim 1, they are also allowable as depending from a nonobvious independent claim 1. (*See*, *In re Fine*, *supra*).

[3] Claims 13-17 depend, directly or indirectly, from independent claim 1 and therefore are also allowable as depending from a nonobvious independent claim. (*See*, *In re Fine*, *supra*).

Group V

Claims 19 and 21 were rejected under 35 U.S.C. § 103(a) over Dellaporta in combination with Koes et al. (*See*, Final Office Action at page 2).

With regard to independent claim 19, the cited references do not teach or suggest each and every limitation of independent claim 19. As previously discussed with reference to claim 1, Dellaporta does not teach or suggest an insertion element library built into a 3D-array of block, row and column pools as also required by claim 19. Further, as previously recited with regard to claim 1, neither Dellaporta nor Koes et al. teach "amplifying each of said plurality of insertion element flanking sequences from said block, row and column pools" as further required by claim 19.

Claim 19 also recites "producing a set of labelled amplification products representing said insertion element flanking sequences derived from said block, row and column pools to use as probes to hybridize to a solid support to which a gene library has been fixed as target(s) for hybridisation, wherein said gene library is organized in at least a two-dimensional array." Dellaporta does not teach screening a **gene library** organized in a two-dimensional array and fixed to a solid support with labeled amplification products as required by claim 19. Rather, Dellaporta discloses "label[ing] the amplified insertion junctions and us[ing] them as probes for the detection of loci corresponding to the insertion mutation" where "a mutation in a specific gene [is screened for with] a cloned DNA segment including that gene sequence as a probe." (Dellaporta, Col. 15, lines 12-14 and lines 52-54). Further, Koes et al. does not teach or suggest producing labeled amplification products to use as probes to hybridize to a gene library fixed on a solid support, but rather is limited to "a method to select transposan insertion mutants for specific genes by a PCR assay." (Koes et al., at p. 8152). Therefore, since neither Dellaporta nor Koes et al., alone or in combination, teach all of the claim limitations of pending independent claim 19, a *prima facie* case of obviousness has not been established. (35 U.S.C. § 103(a)).

Also, as discussed above with reference to claim 1, the Examiner is improperly combining the Dellaporta and the Koes et al. references because there is no suggestion or motivation to combine the teachings of Dellaporta and Koes et al. as asserted by the Examiner, but rather Dellaporta teaches away from the combination of the two references. Thus, a *prima facie* case of obviousness has not

been established with respect to independent claim 19 because there is no suggestion or motivation to combine the teachings of the cited references. (35 U.S.C. § 103(a)).

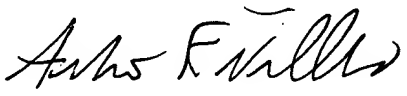
With regard to dependent claim 21, the claim is directed to a kit for performing the method of claim 19. As previously discussed with regard to dependent claims 13-17, since neither Dellaporta nor Koes et al. teach, suggest or motivate a kit and the cited references do not suggest a desirability for modifying the teachings of the cited references to arrive at the claimed invention, a *prima facie case* of obviousness has not been established with regard to claim 21. (*See, In re Gordon, supra*) (35 U.S.C. § 103(a)).

Accordingly, the Examiner has failed to properly establish obviousness under Section 103(a) with regard to claims 1-17 and 19-22, and appellants request the obviousness rejections be withdrawn.

(9) APPENDICES

A copy of claims 1-17 and 19-22 is appended hereto as "APPENDIX A."

Respectfully submitted,



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Enclosures: APPENDIX A - copy of claims 1-17 and 19-22

APPENDIX A

1. A method for simultaneous screening for one or more gene insertion mutants in a population of any organism comprising:

preparing an insertion element mutant library comprising a plurality of nucleic acid insertion elements and insertion element flanking sequences, said insertion element flanking sequences originating from a defined population of an organism wherein said gene insertion mutants are to be detected and wherein said insertion element library is built in a 3D-array of block, row and column pools;

amplifying each of said plurality of insertion element flanking sequences from said block, row and column pools using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements; and

fixing a set of nucleic acid amplification products representing said insertion element flanking sequences derived from said block, row and column pools to a solid support as target for hybridization.

2. The method according to claim 1 wherein the set of nucleic acid amplification products representing said element flanking sequences representing said block, row and column pools are obtained by iPCR using at least one primer or a set of primers based on a sequence of at least one nucleic acid insertion element.

3. The method according to claim 2 wherein said iPCR comprises:

digesting nucleic acid sequences of said block, row and column pools with at least one restriction enzyme resulting in a collection of amplifyable genomic fragments;

ligating at least one amplifyable genomic fragment by self ligation; and

amplifying said at least one amplifyable genomic fragment using a set of internal primers.

4. The method according to claim 3 further comprising reamplifying said at least one amplifyable genomic fragment using at least one primer based on a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements.

5. The method according to claim 1 wherein amplifying

insertion element flanking sequences from said insertion element mutant library built in the 3D-array of block, row and column pools comprises amplifying said insertion element flanking sequences using transposon display amplification.

6. The method according to claim 5 wherein said transposon

display amplification comprises:

generating at least one restriction fragment corresponding to each of said plurality of nucleic acid insertion elements by digesting a plurality of nucleic acid sequences included in said insertion element mutant library using a first restriction enzyme that recognizes six conserved nucleotides and a second restriction enzyme that recognizes a motif of four nucleotides, said at least one restriction fragment including at least a tetracutter site, a

hexacutter site, a part of an insertion element of said plurality of insertion elements, and at least part of an insertion element flanking sequence corresponding to said insertion element;

ligating a biotinylated adaptor to the hexacutter site of each of said at least one restriction fragment as well as a second adaptor to the tetracutter site of said at least one restriction fragmens;

selecting biotinylated restriction fragments using magnetic streptavidin beads;

amplifying insertion element flanking sequences using a primer based on a sequence of the biotinylated adaptor and on the insertion element sequence and a primer complementary to the second adaptor; and

re-amplifying said insertion element flanking sequences using a nested primer based on an insertion element and a primer complementary to the second adaptor.

7. The method according to claim 1 wherein the solid support is a filter, micro-array, or chip containing nucleic acid sequences.

8. The method according toclaim 6 wherein the nucleic acid sequences are selected from a group consisting of genomic DNA and cDNA.

9. The method according to claim 1 wherein preparing the insertion element mutant library comprises preparing an insertion element mutant library including 30 DNA samples from 100 plants each.

10. The method according to claim 9 wherein preparing the insertion element mutant library including 30 DNA samples from 100 plants each comprises preparing an insertion element mutant library built in a 3D array of 10 Block, 10 Row and 10 Column pool each containing DNA of 100 plants characterised by the three coordinates B, R, C.

11. The method according to claim 3 wherein digesting nucleic acid sequences of said insertion element mutant library with at least one restriction enzyme comprises digesting nucleic acid sequences using BfaI as a restriction enzyme.

12. The method according to claim 5 wherein amplifying said insertion element flanking sequences using transposon display amplification comprises using a restriction enzyme selected from a group consisting of MseI and MunI .

13. A kit for performing the method of claim 1 comprising DNA samples of an insertion element mutant library.

14. The kit according to claim 13 further comprising a set of amplified insertion element flanking sequences.

15. The kit according to claim 14 wherein the set of amplified insertion element flanking sequences have been fixed on a solid support, such as a filter, micro-array, or microchip, containing nucleic acid sequences.

16. The kit according to claim 14 wherein the set of amplified insertion flanking sequences is present in a state selected from a group consisting of a soluble state and a dried state.

17. The kit according to claim 16 wherein the set of amplified insertion element flanking sequences are labelled with fluorescein.

19. A method for parallel simultaneous screening for one or more gene insertion mutants in a population of any organism comprising:

preparing an insertion element mutant library comprising a plurality of nucleic acid insertion elements and insertion element flanking sequences, said insertion element flanking sequences originating from a defined population of an organism wherein said gene insertion mutants are to be detected and wherein said insertion element library is built in a 3D-array of block, row and column pools;

amplifying each of said plurality of insertion element flanking sequences from said insertion element mutant library using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements; and

producing a set of labelled amplification products representing said insertion element flanking sequences derived from said block, row and column pools to use as probes to hybridize to

a solid support to which a gene library has been fixed as target(s) for hybridisation, wherein said gene library is organized in at least a two-dimensional array.

20. The method according to claim 2 wherein said iPCR comprises:

digesting nucleic acid sequences of said insertion element mutant library with at least one restriction enzyme which optionally recognizes motifs of four nucleotides in genomic DNA, resulting in a collection of amplifyable genomic fragments;

ligating at least one amplifyable genomic fragment by self ligation; and

amplifying said at least one amplifyable genomic fragment using a primer based on a terminal part of an insertion element.

21. A kit for performing the method of claim 19 comprising DNA samples of an insertion element mutant library.

22. The method according to claim 1 wherein the population is a cell line.

AF# 1600

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Maes et al.

Serial No.: 09/578,361

Filed: May 24, 2000

For: METHOD OF PARALLEL SCREENING FOR INSERTION MUTANTS AND A KIT TO PERFORM THIS METHOD

Confirmation No.: 4901

Examiner: T. Strzelecka

Group Art Unit: 1637

Attorney Docket No.: 2676-4409US

NOTICE OF EXPRESS MAILING

Express Mail Mailing Label Number: EV092481875US

Date of Deposit with USPS: August 19, 2002

Person making Deposit: Jon Wentz

TRANSMITTAL FOR BRIEF ON APPEAL

Commissioner for Patents
Washington, D.C. 20231

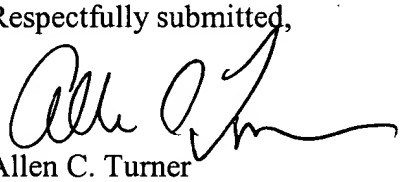
Sir:

Transmitted herewith in triplicate is the BRIEF ON APPEAL in this application with respect to the Notice of Appeal filed on June 19, 2002.

This application is on behalf of a small entity.

The fee for filing an Appeal Brief pursuant to 37 C.F.R. § 1.17(c) of $160.00 is enclosed. Any additional appeal fees which are not otherwise submitted herewith or which are insufficient should be charged to deposit account no. 20-1469. A duplicate copy of this Transmittal is enclosed. Please address all communications in connection with this appeal to the address indicated below.

Respectfully submitted,



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Date: August 19, 2002
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